REMARKS

Entry of the foregoing and reexamination and reconsideration of the subject application, as amended, pursuant to and consistent with 37 C.F.R. § 1.112, are respectfully requested in light of the remarks which follow.

By the foregoing amendment, claim 19 has been canceled without prejudice or disclaimer of the subject matter recited therein. Applicants reserve the right to file a continuation or divisional application directed to any subject matter deleted by way of this Amendment.

Further, claims 1, 27 and 28 have been amended to further clarify Applicants' invention. Support for the amendments can be found throughout the specification and claims as-filed, especially on page 2, line 5, page 3, line 3 and page 11, lines 7-23. Accordingly, no new matter has been added.

Claim Objections

Claim 19 stands objected to under 37 C.F.R. § 1.75(c) as being of improper dependent form for purportedly failing to further limit the subject matter of a previous claim. In the interest of expediting prosecution, claim 19 has been canceled by way of this Amendment. Thus, Applicants respectfully submit that this objection has been traversed.

Claim Rejections under 35 U.S.C. § 112, Second Paragraph

Claims 27 and 28 stand rejected under 35 U.S.C. § 112, second paragraph, as purportedly indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 27 stands rejected under 35 U.S.C. § 112, second paragraph, as indefinite for the recitation of the phrase "the or each series" because the recitation purportedly lacks proper antecedent basis in the preceding "at least one series". Claim 27 has been amended to recite "the series", which has antecedent basis within claim 27. Thus, Applicants respectfully submit that this rejection has been obviated.

Claim 27 stands rejected under 35 U.S.C. § 112, second paragraph, as indefinite for the recitation of the phrase "to relate a terminating. . .of each fragment to the length" because "relate" is purportedly a non-specific relational term. Claim 27 has been amended to further define the relationship between the modified nucleotide or oligonucleotide and the length. Thus, Applicants respectfully submit that this rejection has been obviated.

Claim 28 stands rejected under 35 U.S.C. § 112, second paragraph, as indefinite for the recitation of the phrase "so that each nucleotide is related to a position in the template associated with the mass label" because "related to" and "associated with" are purportedly non-specific relational phrases. Claim 28 has been amended herein to further define the relationship between the template and the label. Thus, Applicants respectfully submit that this rejection has been obviated.

Claim 28 stands rejected under 35 U.S.C. § 112, second paragraph, as indefinite for the recitation of the phrase "the or each series" because the recitation purportedly lacks

proper antecedent basis in the preceding "at least one series". Claim 28 has been amended to recite "the series", which has antecedent basis in claim 28. Thus, Applicants respectfully submit that this rejection has been obviated.

Claim 28 stands rejected under 35 U.S.C. § 112, second paragraph, as indefinite for the recitation of the phrase "wherein the feature of each fragment determined by each mass label" because "the feature" purportedly lacks proper antecedent basis in the claim. Claim 28 has been amended herein to recite "wherein the feature of each fragment identified by each mass label". Thus, Applicants respectfully submit that this rejection has been obviated.

Claim Rejections under 35 U.S.C. § 103(a)

Claim 1 stands rejected under 35 U.S.C. § 103(a) as purportedly obvious over Southern *et al.* (WO 95/04160) in view of Smith (*Nature*, (1991) 349: 812-813). Claims 2-18 and 20-26 stand rejected under 35 U.S.C. § 103(a) as purportedly unpatentable over Southern *et al.* in view of Ness *et al.* (U.S. Patent No. 6,027,890), Alberts (*Molecular Biology of the Cell* (1994) page 298), and Smith. Claim 19 stands rejected under 35 U.S.C. § 103(a) as purportedly unpatentable over Southern *et al.* in view of Smith. Claim 27 stands rejected under 35 U.S.C. § 103(a) as purportedly unpatentable over Southern *et al.* in view of Ness *et al.* and Smith. Claim 28 stands rejected under 35 U.S.C. § 103(a) as purportedly unpatentable over Southern *et al.* in view of Ness *et al.*

In proceedings before the Patent and Trademark Office, the Examiner bears the burden of establishing a *prima facie* case of obviousness based upon the prior art. The

Examiner can satisfy this burden by showing, first, that the cited prior art coupled with the general knowledge at the time of the invention must contain some suggestion or incentive to motivate a skilled artisan to modify or combine references. *See In re Fine,* 837 F.2d 1071, 1074, 5 U.S.P.Q.2d 1596, 1598 (Fed. Cir. 1988); *In re Skinner*, 2 U.S.P.Q.2d 1788, 1790 (Bd. Pat. App. & Int. 1986). Second, the Examiner must show that the modification or combination of prior art references must have a reasonable expectation of success (at the time of the invention). *See Amgen, Inc. v. Chugai Pharm. Co.*, 927 F.2d 1200, 1209, 18 U.S.P.Q.2d 1016, 1023 (Fed. Cir. 1991). Lastly, the Examiner must show that the cited or combined references teach each and every limitation of the claims. *See In re Zurko,* 111 F.3d 887, 888-89, 42 U.S.P.Q.2d 1476, 1478 (Fed. Cir. 1997); *In re Wilson,* 424 F.2d 1382, 1385, 165 U.S.P.Q. 494, 496 (C.C.P.A. 1970). Applicants submit that a case of obviousness has not been adduced.

The Office Action states that relating the feature of each fragment to the length of the fragment is inherent in the method of detecting the mass labels as described in Southern *et al.* Applicants respectfully traverse. The primary reference fails to contain some suggestion or incentive to motivate a skilled artisan to modify or combine references, and the cited references do not recite all of the elements of the claims invention.

Claim 1 has been amended herein to recite "separating the fragments on the basis of their length by capillary electrophoresis". In light of this amendment, Applicants note that fragments of differing lengths, but having the same subsequence, would not be separated in the methods disclosed by Southern *et al.* The Office Action states that relating the feature of the length of the fragment, as recited in claims 1-26 is inherent to the detection of the

mass labels. Applicants submit that this is not the case. Southern *et al.* only discloses using the sequences as a basis for separation. Using the methods disclosed by Southern *et al.*, fragments having the same subsequence would not be separated. In contract, the method of the present invention always separates fragments of different length having the same subsequence.

In light of these remarks and the amendments made herein, Applicants again note that Southern *et al.* do not teach or suggest the use of capillary electrophoresis for the separation of fragments in the same way as the claimed invention, because fragments having the same subsequence cannot be separated. Further, the methods of Southern *et al.* do not determine the length of the labeled template, which corresponds to the DNA being sequenced in the claimed method. In Southern's method, the length of the template must be known in advance, at least to the extent that it must be shorter than an upper limit. The position of oligonucleotide subsequences is inferred from the number of cycles of ligation and the measurements that have already taken place.

Further, Applicants submit that there is no motivation for one of skill in the art to combine the methods of Smith with those of Southern *et al.*, because Smith's article was published in 1991, while the Southern *et al.* patent application was published in 1995, four years later, supposedly as an advance in the field of sequencing.

Double Patenting

Claims 1-24, 27, and 28 stand rejected under the judicially created doctrine of obviousness-type double patenting as purportedly unpatentable over claim 1-21 of U.S.

Patent No. 6,312,904. The Office Action states that although the conflicting claims are not identical, they are purportedly not patentable distinct from each other because both sets of claims are drawn to a method for characterizing nucleic acids and differ only in the arrangement of the limitations within the independent and dependent claims. A Terminal Disclaimer is filed herewith. Thus, Applicants respectfully submit that the double patenting rejections is obviated.

Claims 1-24, 27, and 28 stand rejected under the judicially created doctrine of obviousness-type double patenting as purportedly unpatentable over claim 1-21 of U.S. Patent No. 6,297,017. The Office Action states that although the conflicting claims are not identical, they are purportedly not patentable distinct from each other because both sets of claims are drawn to a method for characterizing nucleic acids and differ only in the arrangement of the limitations within the independent and dependent claims. A Terminal Disclaimer is submitted herewith. Thus, Applicants respectfully submit that the double patenting rejection is obviated

CONCLUSION

In view of the foregoing, further and favorable action in the form of a Notice of Allowance is believed to be next in order. Such action is earnestly solicited.

In the event that there are any questions relating to this application, it would be appreciated if the Examiner would telephone the undersigned attorney concerning such questions so that prosecution of this application may be expedited.

Respectfully submitted,

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Attachment to Amendment and Reply under 37 C.F.R. § 1.111

Marked-up Claims 1, 27 and 28

1. (Thrice Amended) A method for characterizing DNA, which comprises:

(i) providing a population of fragments of said DNA, each fragment having cleavably attached thereto a mass label for identifying a feature of that fragment;

(ii) separating the fragments on the basis of their length by capillary electrophoresis, thereby determining the length of each fragment;

(iii) cleaving each fragment in a mass spectrometer to release its mass label; and

(iv) determining each mass label by mass spectrometry to relate the feature of each fragment to the length of the fragment in order to characterize said DNA.

27. (Twice Amended) A method for characterizing DNA, which comprises:

(a) providing at least one DNA single-stranded template primed with a primer;

(b) generating a population of fragments of said DNA from the at least one template by contacting the at least one template in the presence of DNA polymerase with a mixture of nucleotides for hybridising to the at least one template for forming a second strand of DNA complementary to the at least one template, wherein the mixture further comprises a set of four probes containing all four nucleotides for hybridising to the at least one template in which the nucleotide of each probe comprises a modified nucleotide or oligonucleotide which is capable of polymerising to the second strand of DNA but blocked to prevent further polymerisation thereto, which modified nucleotide or oligonucleotide is cleavably

Attachment to Amendment and Reply under 37 C.F.R. § 1.111

Marked-up Claims 1, 27 and 28

attached to the mass label for identifying the modified nucleotide or oligonucleotide, which mass label is cleavable from the probe in a mass spectrometer and is resolvable by mass spectrometry, and wherein each fragment is terminated with one of the probes, wherein the population comprises at least one series of DNA fragments, the [or each] series containing all possible lengths of a second strand of DNA complementary to the or each template;

(c) separating the fragments by capillary electrophoresis, thereby determining the length of each fragment;

(d) cleaving each fragment in a mass spectrometer to release its mass label; and

(e) determining each mass label by mass spectrometry to identify [relate] a terminating modified nucleotide or oligonucleotide of each fragment by [to] the length of the fragment in order to characterize said DNA.

28. (Amended) A method for characterizing DNA, which comprises:

(a) providing at least one strand of the DNA as a single-stranded template primed with a set of oligonucleotide primers, each of which primers comprises a mass label cleavably attached to an oligonucleotide primer base sequence for hybridising to a single-stranded DNA template to form a primed template, wherein each mass label is cleavable from the primer in a mass spectrometer, uniquely resolvable in relation to every other mass labels in the set by mass spectrometry and identifies the oligonucleotide primer base sequence; and

Attachment to Amendment and Reply under 37 C.F.R. § 1.111

Marked-up Claims 1, 27 and 28

(b) generating a population of fragments of said DNA from the and each template by contacting the and each template in the presence of DNA polymerase with a mixture of nucleotides for hybridising to the and each template for forming a second strand of DNA complementary to the and each template, wherein the population comprises at least one series of DNA fragments, the [or each] series containing all possible lengths of a second strand of DNA complementary to the or each template;

wherein a [the] feature of each fragment identified [determined] by each mass label relates to a nucleotide or nucleotide sequence at one end of each fragment, so that each nucleotide corresponds [is related] to a position in the template primed with the primers comprising the [associated with the] mass label so as to deduce the sequence of the or each template in order to characterise the DNA.